BIOREVOLUTION DEVELOPMENT—INTELLIA'S CRISPR STUDY NEWS

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Intellia Therapeutics, a constituent of the WisdomTree BioRevolution Fund (WDNA), is up 82.27% since announcing positive results from one of its clinical studies.[1] With this tailwind, it is no surprise that the company announced an equity capital raise shortly after the news broke.

For standardized performance of WDNA, please click here.

Before digging into the company-specific details, let's recognize how Intellia's news is one of the many anecdotes driving the BioRevolution.

We are living through exciting times, when the tools of the overlapping genetics and biotechnology frontiers are transforming health care and many other sectors. Although not every new development in these sectors makes widespread waves like the COVID-19 mRNA vaccines produced by Moderna and Pfizer[2], these advancements are happening with increased frequency—and making history. That's why we believe investors could consider reserving a spot in their portfolios for the BioRevolution megatrend.

What Happened with Intellia?

Intellia Therapeutics, in collaboration with Regeneron Pharmaceuticals[3] presented interim data from an ongoing phase 1 clinical study[4] that supported the safety and efficacy of CRISPR[5] genome[6] editing to edit cells inside a human liver, in this case to treat transthyretin amyloidosis (ATTR), a potentially fatal disorder causing nerve and heart disease.

Why Does it Matter?

This is the first human clinical trial using CRISPR therapy administered through a vein to edit genes in the human body to treat disease. The positive results from the study are a significant breakthrough—they provide proof-of-concept for a next generation of CRISPR-based treatments to treat many diseases.

These results are not only important for Intellia but for the broader medical field.

For Intellia, this early-stage success can be leveraged for its other programs and enables expansion of its pipeline in the coming years with increased probability of successful health outcomes and regulatory approval.

For the medical field, this marks the beginning of CRISPR-based therapeutics for broader populations of patients and to address more diseases.

> *…as the first-ever clinical data supporting the safety and efficacy of systemic in vivo CRISPR genome editing, we believe this opens the door to a new era in medicine. We recognize these are interim Phase 1 results, but we believe CRISPR/Cas9 in genome editing more broadly is an immensely powerful tool with vast potential impact. And these results begin to demonstrate that.– John Leonard, Intellia President and Chief Executive Officer*

What is CRISPR?

CRISPR is an acronym for clustered regularly interspace short palindromic repeats. CRISPR is not the first technology that can be used to cut and modify DNA[7], but it is cheaper, faster and more accurate than anything that came before—and genome editing technology is fast improving.

CRISPR-Cas9 was adapted from a naturally occurring defense mechanism from the immune systems of bacteria. The bacteria capture the DNA of viruses and create DNA segments that allow them to later recognize and cut the viral DNA to disable similar viruses.[8] Jennifer Doudna and Emmanuel Charpentier won the 2020 Nobel prize for their role in developing the CRISPR-Cas9 genome editing system. Multiple CRISPR genome editing platforms even more accurate than CRISPR-Cas9 are now under development and in use.

Today, our medical field has adapted that naturally occurring system to develop a new class of therapies for genetics disease. The CRISPR-Cas9 system used by Intellia includes two components: 1) the Cas9 protein, which recognizes and cuts targeted DNA sequences, and 2) the guide RNA[9], which guides the Cas9 protein to the target DNA sequence and activates it to make the cut.[10]

Researchers create guide RNA molecules that program Cas9 to cut DNA at specific locations. This system can be used to edit our DNA in one of three ways: to knock out, repair or insert DNA sequences.

Source: Intellia, https://www.intelliatx.com/crisprcas9/types-of-edits-2/

What Are the Details of the Study?

The disease: ATTR is a progressive and fatal disorder caused by a genetic mutation that results in a misfolded transthyretin (TTR) protein. This causes an abnormal buildup of the protein in organs and tissues that leads to systematic failure.[11] Current treatments slow or halt the progression and symptoms of disease with significant variability and patients require chronic, lifetime dosing to sustain their benefits.

Intellia's treatment: NTLA-2001 is Intellia's ATTR program. It uses CRISPR technology to knock out or disable the gene that causes the TTR protein to misfold. It is the only treatment with curative potential that may both halt and reverse disease progression with a single dose, as opposed to the life-long therapies that are available today.

The results: Six patients received doses of 0.1 milligram per kilogram of body weight (mg/kg) or 0.3 mg/kg. Lower and higher dosage patients had a 52% and 87% reduction in TTR on average, demonstrating a dose-dependent response. Additionally, none of the six patients experienced serious adverse reactions.

Next steps: Further dose escalation is ongoing in the NTLA-2001 program to help identify the recommended dose, and results are expected to be shared in the second half of 2021. After determining dosage, Part 2 of the trial is expected to begin later in 2021, and the objective is to provide an additional clinical assessments and safety data.

Intellia Is But One Example of the Transformative BioRevolution

Jamie Metzl, our third-party collaborator on the WisdomTree BioRevolution Index and a member of the World Health Organization's committee on human genome editing, views the Intellia development as an early indicator of the biology revolution we expect to occur over the coming years.

> *Intellia's success is extremely exciting, but it pales in comparison to the transformative advances across multiple industries we will see as the genetics and biotechnology revolutions play out over the coming years. To quote the classic Bachman-Turner Overdrive song, "You Ain't Seen Nothing Yet."– Jamie Metzl, author of Hacking Darwin: Genetic Engineering and the Future of Humanity and third-party consultant on the WisdomTree BioRevolution Fund*

The intersection of biology and technology transforming health care is also driving transformations across other sectors and industry verticals like agriculture, manufacturing, energy production, consumer services and data storage.

We designed WDNA to provide investors exposure to the revolution occurring within and beyond the medical field. In our view, holding a diverse set of companies, like Intellia, within WDNA allows investors to participate in the incremental changes driving the BioRevolution on a daily basis.

[1]For the period 6/25/21–6/30/21. Double-digit returns are highly unusual and cannot be sustained. Investors should also be aware that these returns were achieved primarily during favorable market conditions.

[2]As of 6/29/21, WDNA held 0.7% and 1.1% of its weight in Moderna, Inc., and Pfizer Inc. respectively.

[3]As of 6/29/21, WDNA held 1.0% and 0.9% of its weight in Intellia Therapeutics, Inc., and Regeneron Pharmaceuticals, Inc., respectively.

[4]A clinical study involves research using human volunteers that is intended to add to medical knowledge. Phase 1 studies focus on the safety of a drug with the goal to determine the drug's most frequent and serious adverse events and how the drug is broken down and excreted by the body.

[5]CRISPR is an acronym for clustered regularly interspaced short palindromic repeats. It is a genome editing technology.

[6]A genome is an organism's complete set of DNA which consists of approximately 3 billion DNA base pairs.

[7]DNA is an acronym for deoxyribonucleic acid, a double-stranded molecule that carries the genetic instructions for all organisms.

[8]Source: "What Are Genome Editing and CRISPR-Cas9?," MedlinePlus. medlineplus.gov/genetics/understanding/genomicresearch/genomeediting/

[9]RNA is an acronym for ribonucleic acid, a single-stranded molecule that is used for a number of different tasks by cells.

[10]Source: "What's CRISPR/Cas9?," Intellia Therapeutics. intelliatx.com/crisprcas9/

[11]Source: "Transthyretin Amyloidosis," MedlinePlus. medlineplus.gov/genetics/condition/transthyretin-amyloidosis/#inheritance

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